Remarks

Amendment to Claims

Claims 1-16, 18-23, and 33-46 have been canceled, without prejudice to Applicants' right to pursue them in one or more continuation, divisional or continuation-in-part applications. Claim 17 has been amended to recite certain indications, which were recited in canceled claim 19. Claims 24 and 27-29 have been amended to correct dependency as claims 18-19 have been canceled. No new matter has been added by these claim amendments.

Accordingly, entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. After the amendments, claims 17 and 24-32 are pending in this application.

The Rejection Under 35 U.S.C. § 112 Should Be Withdrawn

On pages 2-7 of the Office Action, claims 17-19 and 24-32 are rejected under 35 U.S.C. § 112, first paragraph, on the ground that the specification is not enabling for a method of treating a disease ameliorated by the inhibition of PDE4, based on the analysis of factors set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) ("*Wands* factors"). Applicants respectfully traverse this rejection.

Although Applicants strongly disagree with the Examiner's allegation that the specification is viewed as lacking enablement for treatment of any diseases recited (page 2, last paragraph to page 7 of the Office Action), the pending claims have been amended to delete certain indications, solely to expedite the prosecution of the present application, and without prejudice to Applicants' right to pursue them in one or more continuation, divisional or continuation-in-part applications. Indeed, the Examiner himself admitted that the claims are enabled for the treatments of respiratory and inflammatory diseases (page 7 of the Office Action). In view of the amendments and the following discussions, Applicants respectfully submit that the rejection is moot and must be withdrawn.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. Manual of Patent Examining Procedure

(hereafter "MPEP") § 2164.04, (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, "[a] specification disclosure...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Id.* (emphasis added).

The amended claims recite, *inter alia*, methods of treating specific diseases ameliorated by the inhibition of PDE4 in a patient by administering to a patient a therapeutically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof. The specification clearly discloses that the recited diseases can be treated with the recited compound. *See*, for example, page 5, lines 9-24; page 12, line 26 to page 13, line 12; and page 15, line 23 to page 17, line 4.

It is also disclosed that the recited compound can be prepared by synthetic procedures described in Example 2. *See*, the specification, pages 32-40, section 5.2. Dosages and routes of administration of the compound are disclosed, for example, on page 22, line 8 to page 25, line 29 and Examples 7-9 on pages 44-45 of the specification. Therefore, all that is required for those of ordinary skill in the art to practice the claimed invention is to administer the specified amount of the recited compound using the specified routes of administration. In view of the foregoing, the specification provides a sufficient guidance as to treating the recited diseases associated with increased PDE4. Thus, one skilled in the art would have been able to make or use the claimed invention without undue experimentation.

Nonetheless, on pages 3-4, item 3) of the Office Action, the Examiner alleges that there are no disclosures which would enable to identify patients, and predict dosages and routes of administration wherein the compound is to be used for broad indications, that there is no description of any commonality of mechanism of action for the recited drug in the claimed indications, and that none of examples demonstrate each of the treatment as successful. The Examiner further alleges on page 4, item 4) of the Office Action that no guidance is provided in the specification as to treating any/all diseases associated with increased PDE4. It is also alleged that the unpredictability in the pharmaceutical arts regarding dosing, patient sensitivities and modes of administration necessitates further support for enabling the treatment of diseases associated with increased PDE4. (Pages 5-6 of the Office Action). Applicants point out that none of those allegations, alone or in combination, can provide sufficient reason to doubt the fact that the claims are enabled.

Applicants respectfully submit that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." (*See U.S. v. Telectronics, Inc.*, at 785). Further, Applicants respectfully submit that whether the scope of the claim is broad or not is irrelevant to the assessment of the enablement of the claim. The question is whether those skilled in the art would have been able to make and use the claimed invention based on the disclosure. *Id.* Applicant respectfully points out that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. MPEP § 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970)) (emphasis added).

The specification teaches that PDE4 plays a central role in the inflammatory response and that the administration of PDE4 antagonist blocks chronic and acute responses in inflammatory diseases as recited in claim 19. *See, e.g.*, page 2, lines 17-22. Further, the specification discloses that adenosine 3',5'-cyclic monophosphate (cAMP) also plays a role in many diseases and conditions, such as, but not limited to respiratory diseases, asthma and inflammation, and that a primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE). *See, e.g.*, page 3, lines 14-23. The specification and literature references cited in the specification also teach that the inhibition of PDE4 is particularly effective for inhibiting respiratory or inflammatory responses in the diseases. *See, e.g.*, the specification, page 3, lines 14-29. The specification also teaches that the recited diseases are ameliorated by the inhibition of PDE4, and that the diseases can be treated by the administration of PDE4 inhibitor, which is the compound recited in the pending claims. *See, e.g.*, the specification, page 5, lines 9-24; page 12, line 26 to page 13, line 2; and page 21, lines 11-20. In view of the disclosures, the specification provides sufficient description on mechanism of action for the recited compound in the claimed diseases.

Nonetheless, on pages 6-7 of the Office Action, it is alleged that in the specification there are no working examples showing that a representative number of the indications were treated and one skilled in the art would have to undergo an undue amount of experimentation; and that none of the data demonstrate a nexus between the administration of the compound and treatment of the diseases, and a nexus between PDE4 and mechanism of action for the diseases. Applicants respectfully disagree with the allegations.

Applicants emphasize that the specification does indeed include working examples and data. *See*, Examples 1 to 9 on pages 31-45. The specification provides the pharmacokinetic data such as Cmax, Tmax, AUC and plasma concentration data taken at 0.5, 1, 2, 4, 7, 10 and 24 hours following the administration of the recited compound in rats. *See*, the specification, page 43, Example 6, and Figure 1. The specification also discloses that the recited compound has been shown to inhibit PDE4. *See*, specification, page 42, line 10 to page 43, line 4, Examples 4 and 5. The IC_{50} value of the recited compound for PDE4 inhibition was 4.4 μM, as compared to 67 μM and 15 μM of (+) isomer and racemic compound, respectively. *See* Table 1 on page 42. Thus, the specification demonstrates utility that the recited compound is pharmacologically active to inhibit PDE4 and the present claims are enabled.

Applicants point out that the examples and data certainly demonstrate the usefulness of the recited compound for treating the diseases ameliorated by the inhibition of PDE4. The claimed invention is directed to the use of obtainable compound, for which routes of administration and amounts are set forth in the specification on pages 22-25. The skilled artisan can readily determine the IC_{50} for the compound by using the methods described in the specification at page 42. The IC_{50} value one determines is a good indication that the compound is useful in the treatment of the diseases recited in the claims. Moreover, the determination by a physician as to whether the claimed compound is effective in treating the recited diseases, for example, asthma, in a given patient is a type of determination that is always made by physicians for every pharmaceutical. Indeed, the determination is a routine one that every physician is prepared to make, and which requires little or no effort. Therefore, Applicants respectfully submit that one reasonably skilled in the art could make or use the invention as claimed without undue experimentation.

The publications previously submitted also evidence the nexus between the claimed methods and the *in vitro* model for PDE4 inhibition described in the specification (*e.g.*, Example 4 on page 42, lines 10-24). *See, e.g.*, MULLER *et al.*, 1998, "Thalidomide analogs and PDE4 inhibition," *Bioorg. Med. Chem. Lett.*, 2669-2674.

Thus, the specification supports that the correlations between the claimed methods and the studies described in the specification. Therefore, a sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to make and use the claimed invention.

Further, Applicants submit that human working examples for each indication are not required under 35 U.S.C., first paragraph, as explained in MPEP § 2164.02. To the

extent that the IC_{50} data provided in the specification are *in vitro*, Applicants point out that to demonstrate utility, Applicants need only show that any given compound is pharmacologically active *in vitro*. *See Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985) ("Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.) (citations omitted). Further, "[i]f a statement of utility in the specification contains ... a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated," the enablement requirement is satisfied. *Manual of Patent Examination and Procedure* § 2164.01(c) (citing, *inter alia*, *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1993)).

As the Examiner is well aware, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." MPEP § 2164.02 (emphasis added). MPEP § 2164.02 also recognizes that "a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence" (quoting *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)). Where a particular model is recognized as correlating to a specific condition in a given art, the Examiner should accept that correlation, unless the Examiner has evidence that the model does not correlate. (MPEP. § 2164.02; see also *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995)).

Further, Applicant respectfully submits that "compliance with the enablement requirement does not turn on whether an example is disclosed." MPEP § 2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987)). Even in unpredictable arts, a disclosure of every operable species is not required to satisfy enablement. MPEP § 2164.03. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." MPEP § 2164.08. Thus, one of ordinary skill in the art, armed with the information presented in the specification and publication, has adequate guidance to practice the claimed invention.

In sum, Applicants respectfully submit that: (1) the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention; (2) the Examiner did not provide any factual or legal basis to doubt that the claims are enabled; and (3) to the extent any experimentation is necessary, such

experimentation is not undue. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

No fee is believed due for this submission. However, if any fees are required for the entry of this paper or to avoid abandonment of this application, please charge the required fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: February 20, 2007

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THALIDOMIDE ANALOGS AND PDE4 INHIBITION

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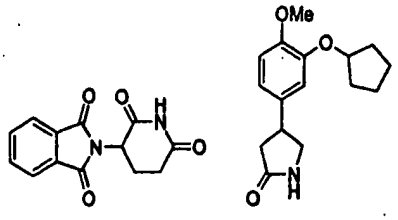
Abstract N-Phthaloyl 3-amino-3-arylpropionic acid analogs of thalidomide that are potent inhibitors of tumor necrosis factor-α are reported. These compounds were found to be potent inhibitors of phosphodiesterase 4.

Introduction

Tumor necrosis factor-α (TNF-α) is a key cytokine in the inflammatory cascade. Excessive TNF-α levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis, Crohn's disease, aphthous ulcers, erythema nodosum leprosum in leprosy, septic shock, cachexia, graft versus host disease, asthma, ARDS, and AIDS.[1] Thus, control of TNF-α levels could be a key to the treatment of a wide range of diseases. The validity of this approach has recently been demonstrated by the clinical benefit observed in the treatment of rheumatoid arthritis and Crohn's disease by TNF-α antibodies and TNF-α soluble receptors.[2] In 1991, thalidomide (1) was reported to be a selective inhibitor of TNF-α production in activated monocytes.[3] Although thalidomide has a tragic history because of its teratogenic properties, it has never totally disappeared from pharmaceutical use because of its effective immunomodulatory properties.[4] In a program to increase the TNF-α inhibitory potency of thalidomide and eliminate/decrease its teratogenic potency we have prepared numerous analogs of thalidomide.



1 5

We recently reported on a series of thalidomide analogs (2 and 3) derived from 3-amino-3-arylpropionic acids, which are potent inhibitors of TNF-α.[5] This series of thalidomide analogs are much more potent inhibitors of TNF-α than thalidomide (TNF-α IC_{50} = ~200 μM)[5]. The mechanism of thalidomide's inhibition of TNF-α levels is unknown, although it was reported by the Kaplan group that it decreases TNF-α mRNA stability.[6] We have continued to explore the mechanism of action of thalidomide and these analogs. It is well documented that elevated levels of cAMP inhibit TNF-α production in activated monocytes and peripheral blood mononuclear

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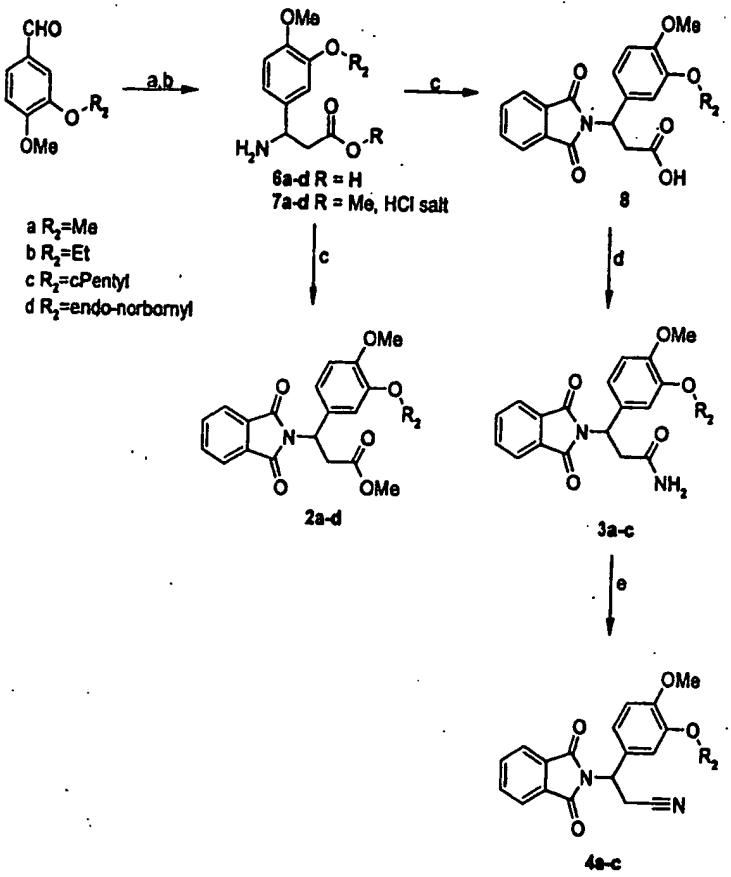
cells (PBMC).[7] Cellular levels of cAMP are controlled by adenylate cyclase and the cAMP phosphodiesterases (PDEs).[8] PDE4 is the major enzyme found in monocytes, the major producers of TNF-α in the inflammatory cascade. Inhibition of PDE4 has been shown to be an effective method for inhibition of TNF-α production in activated monocytes and PBMC. We wish to report the discovery that these thalidomide analogs (2 and 3) and the related nitriles (4) are potent inhibitors of PDE4.

Scheme 1



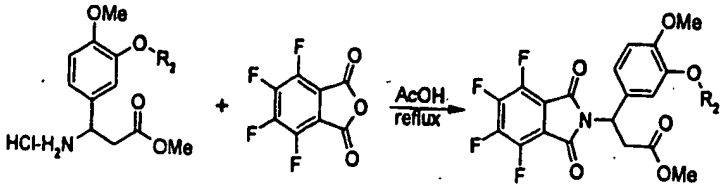
Regents: (a) NH_4OAc, $CH_2(CO_2H)_2$, EtOH, reflux; (b) $SOCl_2$/MeOH; (c) N-carbethoxyphthalimide, Na_2CO_3, CH_3CN/H_2O; (d) (1) CDI/THF, (2) concentrated NH_4OH; (e) $SOCl_2$ or $(COCl)_2$/DMF/pyridine.

Chemistry

The ester and amide analogs were prepared as previously described (Scheme 1).[5] The nitrile analogs were prepared from the corresponding amides. 3-Amino-3-arylpropionic acids were prepared as previously described by treatment of a substituted benzaldehyde with malonic acid and ammonium acetate in refluxing EtOH. Substituted 3,4-dialkoxybenzaldehydes were commercially available or prepared as previously described.[9] The N-phthaloyl carboxylic acids (8a-c) were prepared using a standard Nef reaction. The N-

phthaloyl carboxylic methyl esters **2a-d** were prepared by conversion of the 3-amino-3-arylpropionic acid (**6a-d**) to the methyl esters (**7a-d**) by treatment with $SOCl_2$ in MeOH, followed by treatment with Nef's reagent in the presence of Na_2CO_3 (Scheme 1). Conversion of phthaloyl carboxylic acids (**8a-c**) to the corresponding phthaloyl amides (**3a-c**) was accomplished by activation of the carboxylic acid with carbonyldiimidazole (CDI) followed by treatment with conc. NH_4OH. The amides **3a-c** were dehydrated to the nitriles with $SOCl_2$ or $(COCl)_2$.[10] The tetrafluorophthaloyl analogs **9a** and **9b** were prepared by condensation of **7a** and **7b**, respectively with tetrafluorophthalic anhydride in refluxing acetic acid (Scheme 2).

Scheme 2



9a R_2=Me
9b R_2=Et

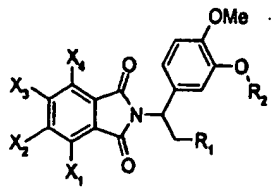
Biological Assays

TNF-α inhibitory activity was measured in lipopolysacharide (LPS) stimulated PBMC as previously reported.[5] Crude PDE4 extract was obtained from U937 cells using the method of Hill and Mitchell as described below.[11] Cells (1×10^9) were washed in PBS and lysed in cold homogenization buffer (20 mM Tris-HCl, pH 7.1, 3 mM 2-mercaptoethanol, 1 mM $MgCl_2$, 0.1 mM EGTA, 1 μM PMSF, 1μg/mL leupeptin). Following homogenization in a Dounce homogenizer the supernatant was collected by centrifugation and loaded onto a Sephacryl S-200 column equilibrated in homogenization buffer. PDE was eluted in homogenization buffer and the rolipram sensitive fractions pooled and stored in aliquots. PDE activity was assayed using the protocol adapted from Hill and Mitchell[11] and based on assay described by Thompson et al.[12] Enzyme activity was assayed in 50 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$ and 1 μM cAMP (of which 1% was ^3H cAMP) in the presence of varying concentrations of inhibitors. The amount of extract used was pre-determined to ensure that reactions were within the linear range and consumed less than 15% of the total substrate. Reactions were performed at 30 °C for 30 min and terminated by boiling for 2 min. The samples were then chilled and treated with snake venom (1 mg/mL) at 30 °C for 15 min. Unused substrate was removed by incubation with 200 μL AG1-X8 resin (BioRad) for 15 min. Samples were then spun at 3000 rpm for 5 min and 50 μL of the aqueous phase taken for counting. Each data point was carried out in duplicate with activity expressed as percentage of control. IC_{50}s was determined from dose response curves derived from three independent experiments. TNF-α and PDE4 IC_{50}s were calculated by non-linear regression analysis (variable slope) using Prism by GraphPad Software, Inc.

Results and Discussion

These thalidomide analogs were screened for their ability to inhibit TNF-α in LPS stimulated human PBMC.[5] PDE4 inhibitory activity was assayed with PDE4 enzyme isolated from the U937 cells, a promonocytic cell line. A good correlation between TNF-α inhibition and PDE4 inhibition was observed for the majority of compounds (Table 1). Thalidomide was inactive in the PDE4 assay (IC_{50} > 500 μM). A separation in mechanism of action between these analogs and thalidomide was found. These compounds appear to inhibit TNF-α by elevation of cellular cAMP levels.

Table 1: TNF-α and PDE4 Inhibition by Thalidomide



compd	R_2	R_1	X_1	X_2	X_3	X_4	TNF-α IC_{50} [μM]	PDE4 IC_{50} [μM]
2a	Me	CO_2Me	H	H	H	H	2.9	2.5
2b	Et	CO_2Me	H	H	H	H	0.70	0.23
2c	cPentyl	CO_2Me	H	H	H	H	1.6	1.7
2d	norbornyl	CO_2Me	H	H	H	H	2.4	0.74
3a	Me	$CONH_2$	H	H	H	H	13	9.4
3b	Et	$CONH_2$	H	H	H	H	2.7	2.0
3c	cPentyl	$CONH_2$	H	H	H	H	2.5	1.1
4a	Me	CN	H	H	H	H	1.7	1.3
4b	Et	CN	H	H	H	H	0.12	0.13
4c	cPentyl	CN	H	H	H	H	1.6	0.35
9a	Me	CO_2Me	F	F	F	F	0.26	4.7
9b	Et	CO_2Me	F	F	F	F	0.38	2.2

The prototypical PDE4 inhibitor, rolipram (PDE4 IC_{50}= 0.40 μM and TNF-α IC_{50}= 0.15 μM),[13] 5 contains a 3-cyclopentoxy-4-methoxyphenyl moiety, which correlated with the 3,4-dimethoxypheny moiety found in these thalidomide analogs. The SAR of the 3,4-dialkoxyphenyl moiety in rolipram type PDE4 inhibitors is well developed. A 3-cyclopentoxy-4-methoxyphenyl moiety along with other large hydrophobic 3-

alkoxy substituents such as endo-norbornyloxy is preferred.[14] The SAR of the 3-alkoxy group was explored in this series (Table 1). Interestingly, these PDE4 inhibitors do not directly follow the SAR of known rolipram type analogs. The 3-cyclopentoxy-4-methoxyphenyl analog **2c** was only 2-fold more active as a PDE4 inhibitor than the previously reported 3,4-dimethoxy analog **2a**. The 3-ethoxy-4-methoxy analog **2b** was over 7-fold more active as a PDE4 inhibitor than **2c**. The differences in TNF-α inhibitory activities were smaller but followed the same trend. The smaller differences in the TNF-α inhibitory potencies are probably due to cell based effects of the TNF-α inhibition in which the compound must enter the cell to be active. In the amide series, the 3-cyclopentoxyl analog **3c** was 2-fold more active than the 3-ethoxy analog **3b** and a magnititude more active as a PDE4 inhibitor. However, **3b** and **3c** were equipotent as TNF-α inhibitors. Isosteric replacement of the amide/ester moiety with a nitrile was investigated. The nitriles **4a-c** were significantly more potent as PDE4 inhibitors than the amide analogs but afforded only slight improvements over the ester analogs. The 3-ethoxy-4-methoxy nitrile is the most potent TNF-α inhibitor of the reported compounds with an IC_{50} of 120 nM. In this series of compounds the smaller 3-ethoxy substituent appears to be preferred over larger 3-alkoxy substituent.

Recently other researchers reported the tetrafluorophthaloyl analog of **3a** as a potent TNF-α inhibitor in LPS stimulated THP-1 cells.[15] We also prepared this compound, **9a** and the 3-ethoxy-4-methoxy analog **9b** and found them to be potent inhibitors of TNF-α in LPS stimulated PBMC (Table 1). However, both compounds were found to be cytotoxic at 10 and 100 μM in this assay which put the TNF-α inhibition results in question.[16] The non-fluorinated analogs described were not cytotoxic at the highest concentration (100 μM) tested in this assay. Both **9a** and **9b** were found to be approximately 10- to 15-fold less active as PDE4 inhibitors compared to their TNF-α inhibitory activity. Whether the differences in the TNF-α and PDE4 inhibitory activity are due to the cytotoxicity of the compounds in the TNF-α inhibition is unknown.

In conclusion, we have determined that these thalidomide analogs are potent inhibitors of PDE4. It is proposed that these thalidomide analogs control TNF-α levels by inhibition of PDE4. Thalidomide was found to be inactive against PDE4 (IC_{50} > 500 μM). Although thalidomide was inactive against PDE4 the possibility that one or more of its metabolites or degradation products inhibits PDE4 has not been eliminated. Using thalidomide as a lead structure we have discovered a novel series of potent PDE4 inhibitors. The most active compound reported here is >1,500 times more potent (IC_{50}) as a TNF-α inhibitor than thalidomide. Future publications from our laboratories will further describe the SAR and report the potential therapeutic value of these PDE4 inhibitors.

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